REMARKS

This paper is being presented in response to the non-final official action dated October 19, 2005, wherein all of the pending claims (i.e., claims 1-17 and 32-40) have been have been rejected under 35 USC § 112, ¶ 1, as allegedly lacking an enabling disclosure. Reconsideration and withdrawal of the rejection are respectfully requested in view of the foregoing amendments and following remarks.

I. Brief Summary of the Amendments

The specification has been amended, claims 13 and 32-38 have been canceled, claims 1-9, 12, 14-17, 39, and 40 have been amended, and claims 54-67 are being newly added by this paper.

A. Amendments to the Specification

The title of the application has been amended to be consistent with the claims.

The cross-reference to related applications has been updated.

The "Abstract of the Disclosure" has been amended pursuant to the statements set forth at page 2 of the action, and now reads:

> Disclosed herein are methods of treating an individual suffering from peripheral neuropathy. The methods generally include administration of a therapeutic amount of optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof. Embodiments of these methods can diminish adverse side effects.

B. Amendments to the Claims

Dependent claim 13 has been canceled. Independent claim 1 has been amended to incorporate the subject matter originally recited in now-canceled, dependent claim 13. Claim 1 also has been amended to recite the administration of "a therapeutically effective amount of optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof," to an individual suffering from peripheral neuropathy. Support for this amendment can be found in the specification at, for example, page 9, lines 14-17, and page 15, lines 16-28.

Dependent claims 2-8 have been amended to clarify that it is the optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof, that is administered in the recited amounts. Support for the amendments to these claims can be found in the specification at, for example, page 24, line 12, to page 25, line 3.

Dependent claim 9 has been amended to recite that optically pure (S,S) reboxetine is administered as a composition. Support for the amendment can be found in the specification at, for example, page 18, lines 20-21, and page 22, lines 1-16.

Dependent claim 12 has been amended to correct a typographical error in the spelling of the term "intravenously."

Claims 14 and 15, previously dependent upon claim 13, have been amended to now depend from amended claim 1.

Dependent claims 15-17 have been amended to clarify that the percentages recited therein are based upon the total amount of reboxetine present. Support for the amendments to these claims can be found in the specification at, for example, page 16, lines 22 and 23.

In addition to claim 13, claims 32-38 have been canceled herein without prejudice to filing a continuing application directed to the subject matter of these claims.

Independent claim 39 has been amended to improve its clarity by removing the redundant recitation "said optically pure (S,S) reboxetine being substantially free of (R,R) reboxetine." Support for the amendment can be found in the specification at, for example, page 16, lines 10-13.

Dependent claim 40 has been amended to replace "and" with "or." Support for the amendment can be found in the specification at, for example, page 17, lines 22-27, and page 21, lines 17-22.

Claims 54-67 have been added herein and are either directly or indirectly dependent upon claim 39. Claims 54-67 recite features similarly recited in dependent claims 3-12 and 14-17.

No new matter has been introduced by this paper.

By the foregoing amendments, fourteen dependent claims are being newly-added and seven dependent claims are being cancelled. Accordingly, submitted herewith is a check in the amount of $350.00 to cover the fee set forth at 37 CFR § 1.16(i) for examination of seven claims in excess of twenty.

II. The 35 USC § 112, ¶ 1, Rejection is Traversed

The pending claims have been rejected under 35 USC § 112, ¶ 1, as allegedly lacking an enabling disclosure. *See* the Action at pp. 2-5. A response to the rejection is set forth below.

A. Proper Basis for a § 112, ¶ 1, Lack of Enablement Rejection

The patent statute requires that a patent application include a specification containing a written description of the manner and process of making and using the claimed invention in such full, clear, concise, and exact terms as to enable any person skilled in the art to which the invention is most nearly connected to make and use the claimed invention. *See* 35 USC § 112, ¶ 1. Even though the statute does not use the term "undue experimentation," it has

been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the claimed invention without undue experimentation. *In re Wands*, 858 F.2d, 731, 737, (Fed. Cir. 1988). If such a skilled person could make and use the claimed invention from the description set forth in the specification coupled with information known in the art, without undue experimentation, then the specification satisfies the patent statute's enablement requirement. *See United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988); *see also In re Angstadt*, 537 F.2d 498, 504 (CCPA 1976) (stating the test of enablement is *not* whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue).

There are many factors to be considered when determining whether there is sufficient evidence to support a conclusion that a patent application does not satisfy the enablement requirement, and whether any necessary experimentation is "undue." The action (at page 3) correctly acknowledges these factors, which include:

(a) Breadth of the claims and nature of the invention;

(b) Relative skill of those in the art, state of the art, and level of predictability or unpredictability in the art;

(c) Amount of direction or guidance provided and presence or absence of working examples; and,

(d) Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See In re Wands, 858 F.2d at 737. It is improper to conclude that a patent application is not enabling based on an analysis of only one of the foregoing factors, while ignoring one or more of the other factors—a conclusion of non-enablement must be based on the evidence as a whole. *See id.* at 740.

The U.S. Patent and Trademark Office ("Patent Office") bears the burden to establish a reasonable basis to question the enablement the patent application provides for the claimed invention. *See In re Wright*, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993) (stating that the Patent Office must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A disclosure teaching how to make and use an invention in terms corresponding in scope to those defining the claimed subject matter complies with the enablement requirement (in § 112, ¶ 1), *unless* there is a reason to doubt the objective truth of the disclosure relied upon for enabling support. A rejection for a failure to teach how to make and use the claimed invention will be proper if sufficient reason(s) for such doubt exists:

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis [i.e., non-enablement] is made, to explain why it

> doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

In re Marzocchi, 439 F.2d 220, 223-24 (CCPA 1971).

After the Patent Office has established a reasonable basis to question the enablement provided for the claimed invention, the burden falls on the patent applicants to present persuasive arguments, supported by suitable proofs where necessary, that a person skilled in the art would have been able to make and use the claimed invention using the patent application as a guide. *See In re Brandstadter*, 484 F.2d 1395, 1406 (CCPA 1973). For example, the applicants may attempt to overcome the Patent Office's doubt about enablement by explaining teachings set forth in the patent application; however, the applicants may not add new matter. Furthermore, the applicants also may submit factual affidavits under 37 CFR § 1.132, or identify publications, demonstrating what a person skilled in the art would have known as of the patent application's filing date. In determining (and reconsidering) whether the patent application includes an enabling disclosure of the claimed invention, the Patent Office shall consider all evidence in the record (including the patent application), weighing evidence that confirms enablement against evidence that refutes enablement. *See In re Wands*, 858 F.2d at 737, 740.

B. The Specification Provides a Disclosure Satisfying § 112, ¶ 1

Set forth below, is the applicants' position that the patent application contains a written description of the manner and process of making and using the claimed invention in such full, clear, concise, and exact terms as to enable any person skilled in the art to which the invention is most nearly connected to make and use the claimed invention in compliance with § 112, ¶ 1. Specifically, subsection 1, below, describes the Patent Office's and the applicants' positions relative to each of the *Wands* factors. Subsection 2, below, describes post-application filing evidence demonstrating the claimed methods are effective and can diminish adverse side effects. Subsection 3, below, presents arguments traversing the rejection.

1. The Wands Factors

(a) Breadth of the Claims and Nature of the Invention

The specification describes methods of treating a variety of human conditions wherein selective, specific, and potent inhibition of norepinephrine reuptake provides a benefit. The Specification at p. 9, line 14. One such condition is peripheral neuropathy. *See, e.g., id.* at p. 10, line 26, p. 18, lines 20-22, and p. 19, lines 10-11. These methods include

those recited in the pending claims, the text of each of which is reproduced above. Of the pending claims, claims 1 and 39 are the only independent claims:

> **1.** A method of treating an individual suffering from peripheral neuropathy, the method comprising the step of administering to the individual a therapeutically effective amount of optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof.
>
> **39.** A method of treating an individual suffering from peripheral neuropathy while diminishing adverse side effects, the method comprising the step of administering to the individual a total dose of about 0.1 to about 10 mg/day of an optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof.

(As amended, the pending claims do not recite methods of *preventing* peripheral neuropathy.) Because the action sets forth no independent bases for questioning the enablement of any of the dependent claims, the enablement rejection is addressed relative to the breadth of the claims as defined by independent claims 1 and 39.

In view of the claim amendments presented herein, the nature and breadth of the claimed invention relate to methods of treating an individual suffering from peripheral neuropathy. These methods include administering a therapeutically effective amount of optically pure (S,S) reboxetine (or a pharmaceutically acceptable salt thereof) to the individual. *See, e.g.*, claim 1. Embodiments of these methods can diminish adverse side effects, when, for example, a total dose of about 0.1 to about 10 mg/day of optically pure (S,S) reboxetine (or a pharmaceutically acceptable salt thereof) is administered to the individual. *See, e.g.*, claim 39. The specification defines a number of claim terms including, but not limited to, "reboxetine" (page 16, lines 6-9), "optically pure (S,S) reboxetine" (page 16, lines 10-27), "pharmaceutically acceptable salts" (page 16, line 28, to p. 17, line 21), "adverse side effects" (page 17, lines 22-27), and "treating" (page 17, line 28 to p. 18, line 13).

The specification also describes *how to make* optically pure (S,S) reboxetine (and a composition containing the same and/or a pharmaceutically acceptable salt thereof) used in the recited treatment methods at, for example, page 22, line 1, to page 24, line 11. Furthermore, the specification describes *how to practice* the claimed methods by specifying desirable and preferable daily doses at, for example, page 24, line 12, to page 25, line 3. The specification further states, at p. 25, line 29, to p. 26, line 2, that "the optimum daily dosage for each patient must be determined by a treating physician taking into account each patient's size, other medications which the patient is taking, identity and severity of the disorder, and all of the other circumstances of the patient."

Having described how to make the composition recited in the claimed methods and how to practice these methods, the specification also describes advantages the invention

provides over certain prior art such as, for example, reduced dosages and reduced adverse side effects:

> Optically pure (S,S) reboxetine is advantageous over prior, treatment or prevention methods which utilized a racemic mixture of (R,R) and (S,S) reboxetine. In particular, it has been found that treatments using compositions containing an optically pure (S,S) reboxetine are about 5 to about 8.5 times more effective at inhibiting the reuptake of norepinephrine than compositions containing the racemic mixture of the (R,R) and (S,S) stereoisomers. Therefore, reuptake blockage can be achieved with much lower dosages. Accordingly, the present invention may permit a substantial reduction in the customary daily dosage of the racemic mixture (i e., the commercially available reboxetine) by about 50% to about 80% because of the use of an optically pure (S,S) reboxetine. In addition, treatments utilizing the optically pure (S,S) reboxetine may result in fewer undesirable adverse side effects associated with the treatment because of the high selectivity and potency of (S,S) reboxetine with respect to inhibiting the reuptake of norepinephrine.

Id. at p. 11, line 28, to p. 12, line 13.

The specification, thus, describes the breadth and nature of the claimed invention, specifically identifying a substantial reduction in the customary daily dosage of commercially-available racemic reboxetine when using an optically pure (S,S) reboxetine, and teaches that the claimed treatment methods may result in fewer undesirable adverse side effects associated with the treatment because of the high selectivity and potency of (S,S) reboxetine with respect to inhibiting the reuptake of norepinephrine.

(b) Relative skill of those in the art, state of the art, and level of predictability or unpredictability in the art

The action (p. 4) alleges that the level of skill in the art is generally that of "a Ph.D. or M.D. with expertise in the area of neurology." The applicants do not dispute this allegation. However, the applicants submit that an example of a Ph.D. with expertise in the area of neurology is a person having a Ph.D. in pharmacology and experience in the neurosciences.

The action (p. 4) alleges that the prior art "does not presently recognize methods of preventing peripheral neuropathy or means of diminishing the side effects of reboxetine therapy," that "this particular art is immature" and, therefore, "a more detailed description as to the means of practicing the claimed methods would reasonably be expected."

The specification describes portions of the background of the claimed invention as follows:

> Currently, reboxetine is commercially available only as a racemic mixture of enantiomers, (R,R) and (S,S) in a 1:1

ratio, and reference herein to the generic name "reboxetine" refers to this enantiomeric, or racemic, mixture. Reboxetine is commercially sold under the trade names of EDRONAX™, PROLIFT™, VESTRA™, and NOREBOX™. As previously noted, reboxetine has been shown to be useful in the treatment of human depression. Orally administered reboxetine is readily absorbed and requires once or twice a day administration. A preferred adult daily dose is in the range of about 8 to about 10 milligrams (mg). The effective daily dosage of reboxetine for a child is smaller, typically in a range of about 4 to about 5 mg. The optimum daily dosage for each patient, however, must be determined by a treating physician taking into account the patient's size, other medications which the patient may be taking, identity and severity of the particular disorder, and all of the other circumstances of the patient.

Administration of reboxetine, however, can result in undesired side effects associated with drug-drug interactions and in other undesirable effects such as, for example, dizziness, insomnia, lightheadedness, changes in blood pressure, sweating, gastrointestinal disturbances, sexual dysfunction in males, certain anticholinergic-like effects (e.g., tachyardia and urinary retention). It has been found that such side effects occur, in part, because reboxetine lacks a sufficiently high selectivity for inhibiting norepinephrine reuptake. In other words, reboxetine is blocking reuptake of other monoamines, like serotonin and dopamine, to a sufficient degree to contribute to the undesired side effects.

It has been reported that other antidepressants have a high pharmacological selectivity for inhibiting reuptake of norepinephrine. For example, oxaprotiline has a pharmacological selectivity with respect to inhibiting norepinephrine reuptake compared to serotonin reuptake of about 4166, based on a ratio of K_i values. The corresponding pharmacological selectivity for desipramine is about 377, and that for maprotiline is about 446. See Elliott Richelson and Michael Pfenning, "Blockade by Antidepressants and Related Compounds of Biogenic Amine Uptake in Rat Brain Synaptosomes: Most Antidepressants Selectively Block Norepinephrine Uptake," European Journal of Pharmacology, vol. 14. pp. 277-286 (1984). Despite the relatively high selectivity of oxaprotiline, desipramine, and maprotiline, these and other known materials undesirably block receptor of other neurotransmitters to a sufficient degree that they also contribute to adverse side effects.

Accordingly, there is a need in the art for a method of treating individuals suffering from a variety of conditions where inhibiting reuptake of norepinephrine provides a benefit, while reducing or eliminating the adverse side effects associated with conventional norepinephrine reuptake inhibitors. There also is a need for a method that selectively inhibits the reuptake of norepinephrine over other neurotransmitters, like serotonin and dopamine. Specifically,

> there is a need in the art for a highly selective (at one reuptake site), specific (with no activity at other receptors), and potent norepinephrine reuptake inhibitor. Furthermore, there is a need for pharmaceutical compositions containing a highly selective and potent norepinephrine reuptake inhibitor. Still further, there is a need for medicaments containing such pharmaceutical compositions, and the use of such compositions in the manufacture of such medicaments.

See the Specification at p. 7, line 17, to p. 9, line 7. The specification, thus, states a racemic mixture of the (R,R) and (S,S) enantiomers of reboxetine has been shown to be useful for the treatment of depression. Administration of, and dosing regimens with, this mixture also are known in the prior art. As set forth in more detail in the following subsection, the specification describes how to make a pharmaceutical composition containing (S,S) reboxetine and how to practice the claimed methods by specifying desirable and preferable dosing regimens.

(c) Amount of direction or guidance provided and presence or absence of working examples

The action states the following:

> Applicants have failed to provide support for the efficacy in the treatment or prevention of peripheral neuropathy, and diminishing adverse side effects following administration of (S,S) reboxetine. The skilled artisan would expect the interaction of a particular compound in the prevention or treatment of this particular neurological disorder to be very specific and highly unpredictable absent a clear understanding of the structural and biochemical basis for the administration of a particular compound. The instant specification sets forth no such understanding. No direction is provided to distinguish therapy among the various side effects.

See the Action at pp. 4-5. The action (p. 4) also states that the patent application provides neither "working examples directed to the treatment or prevention of peripheral neuropathy," nor "examples to support or suggest a successful therapeutic regimen."

As previously identified herein, the specification identifies (S,S) reboxetine as a specific, selective, and potent norepinephrine reuptake inhibitor and states that such inhibitors are useful to treat a number of disorders including peripheral neuropathy. The specification also discloses how to prepare a pharmaceutical composition containing (S,S) reboxetine and describes desirable and preferable daily doses of the composition:

> Desirably, daily dose of the composition (e.g., tablet, sachet, or capsule) contains from about 0.1 to about 10 mg of optically pure (S,S) reboxetine, and is substantially free of its (R,R) stereoisomer. More preferably, each dose of the composite contains about 0.5 to about 8 mg of the active ingredient, optically-pure (S,S) reboxetine, and is substantially free of its (R,R) stereoisomer. Even more

> preferably, however, each dose contains from about 0.5 to about 5 mg of the active ingredient, such as an optically-pure (S,S) reboxetine, and is substantially free of its (R,R) stereoisomer. This dosage form permits the full daily dosage of about 0.5 to about 2.5 mg to be administered in one or two oral doses. This will allow for tablets containing 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, or 2.5 mg of optically pure (S,S) reboxetine.
>
> In another embodiment, a preferred daily dose of the composition (e.g., tablet, sachet, or capsule) contains from about 0.1 to about 0.9 mg of optically pure (S,S) reboxetine, and is substantially free of its (R,R) stereoisomer. More preferably, each dose of the composition contains about 0.5 to about 0.8 mg of the active ingredient, optically-pure (S,S) reboxetine, and is substantially free of its (R,R) stereoisomer. Even more preferably, however, each dose contains from about 0.5 to about 0.75 mg of the active ingredient, optically pure (S,S) reboxetine, and is substantially free of its (R,R) stereoisomer. This dosage form permits the full daily dosage of about 0.5 to about 0.9 mg to be administered in one oral dose.

The Specification at p. 24, line 12, to p. 25, line 3. The specification further states that "the optimum daily dosage for each patient must be determined by a treating physician taking into account each patient's size, other medications which the patient is taking, identity and severity of the disorder, and all of the other circumstances of the patient."

The specification also identifies common adverse side effects that can be diminished when practicing embodiments of the claimed methods:

> The phrases "side effects," "adverse effects," and "adverse side effects" in relation to reboxetine include, but are not limited to, dizziness, insomnia, lightheadedness, changes in blood pressure, gastrointestinal disturbances, sexual dysfunction in males, extrapyramidal side effects, certain anticholinergic-like effects (e.g., tachycardia, blurred vision), and undesired side effects associated with drug-drug interactions.

Id. at p. 17, lines 22-27. Furthermore, the specification describes that (S,S) reboxetine selectively interacts with the norepinephrine reuptake site (relative to the serotonin reuptake site):

> In particular, because an optically pure (S,S) reboxetine selectively inhibits norepinephrine reuptake compared to serotonin reuptake, adverse side effects associated with serotonin reuptake are reduced or eliminated. Such adverse side effects include, but are not limited to, gastrointestinal disturbances, anxiety, sexual dysfunction, and undesirable side effects associated with drug-drug interactions.

Id. at p. 21, lines 17-22. The specification also includes an example demonstrating the superior pharmacological selectivity and potency of (S,S) reboxetine compared to its stereoisomer and to racemic reboxetine, dispelling any unpredictability that might be present in the mind of a person having a Ph.D. in pharmacology and expertise in the neurosciences:

> The surprisingly high potency of the (S,S) enantiomer over both the racemic reboxetine and (R,R) reboxetine provides a treating physician an ability to prescribe an effective dosage of a norepinephrine reuptake inhibitor, i.e., (S,S) reboxetine, that is about 10% to about 20% of the current daily dosage of reboxetine (racemate) to achieve the same reuptake inhibition at the norepinephrine site. In addition, the surprisingly high inhibition selectivity of an optically pure (S,S) reboxetine essentially limits inhibition to norepinephrine reuptake, thereby reducing adverse side effects associated with inhibition at serotonin reuptake sites and blockade at other receptors.

Id. at, p. 29, line 20, to p. 32, line 24.

(d) Quantity of Experimentation Necessary to Make or Use the Invention Based on the Content of the Disclosure

According to the action:

> Absent reasonable *a priori* expectations of success for *preventing* any peripheral neuropathy and diminishing adverse effects, one skilled in the art would have to test extensively many adverse outcomes of therapy to discover which particular side effects respond to (S,S) reboxetine therapy. Since each prospective embodiment, as well as future embodiments as the art progresses, would have to be empirically tested, undue experimentation would be required to practice the invention as it is claimed in its current scope. The specification provides inadequate guidance to do otherwise.

See the Action at p. 5 (emphasis added). The specific statement relates to subject matter (preventing peripheral neuropathy) not recited in the pending claims. To the extent that it relates to subject matter recited in the pending claims (e.g., treating peripheral neuropathy while diminishing adverse side effects), the specification describes adverse side effects associated with, for example, serotonin reuptake and with administration of commercially-available (racemic) reboxetine. *See generally*, Sections II.B.1(b) and II.B.1(c), above.

The application clearly teaches that (S,S) reboxetine exhibits little interaction (relative to a racemic reboxetine) at the serotonin site and, therefore, would not trigger effects known to be associated with inhibition of serotonin reuptake:

> The surprisingly high potency of the (S,S) enantiomer over both the racemic reboxetine and (R,R) reboxetine provides a treating physician an ability to

> prescribe an effective dosage of a norepinephrine reuptake inhibitor, i.e., (S,S) reboxetine, that is about 10% to about 20% of the current daily dosage of reboxetine (racemate) to achieve the same reuptake inhibition at the norepinephrine site. In addition, the surprisingly high inhibition selectivity of an optically pure (S,S) reboxetine essentially limits inhibition to norepinephrine reuptake, thereby reducing adverse side effects associated with inhibition at serotonin reuptake sites and blockade at other receptors.

The Specification at, p. 29, line 20, to p. 32, line 24. According to the application, effects believed to be associated with inhibition of serotonin reuptake include, but are not limited to, dizziness, insomnia, lightheadedness, changes in blood pressure, gastrointestinal disturbances, sexual dysfunction in males, extrapyramidal side effects, certain anticholinergic-like effects (e.g., tachycardia, blurred vision), and undesired side effects associated with drug-drug interactions. *Id.* at p. 17, lines 22-27. Thus, the application describes particular effects responsive to (S,S) reboxetine therapy (i.e., treatment of peripheral neuropathy) and identifies common side effects, which the claimed invention would not cause.

2. Post-Application Filing Evidence of Enablement

Since this application and the priority benefit applications have been filed, the assignee of the applications has performed further experimental work, some of which is described in the following subsections. Specifically, the assignee has performed studies comparing the selectivity of (S,S) reboxetine with the selectivity of other compounds (*see* subsection (a), below), and clinical studies reviewing and comparing patient-tolerability of (S,S) reboxetine versus racemic reboxetine (*see* subsection (b), below).

(a) The Arneric Declration

Attached hereto as Appendix "A" is a copy of a "Declaration of Stephen P. Arneric Pursuant to 37 C.F.R. § 1.132" (the "Arneric Declaration"), which was filed in and during prosecution of the grandparent application (U.S. Serial No. 09/599,213, now U.S. Patent No. 6,465,458). Although the declaration was submitted in connection with the grandparent application, the specification of the grandparent application is identical to that of the present application and, therefore, the disclosed subject matter is identical.

Paragraphs 1 and 4-6 of Dr. Arneric's declaration describe his background (including a Ph.D. degree in Pharmacology and work experience in the neurosciences) and demonstrate that he is qualified to comment on the subject matter disclosed in the current application. Paragraphs 8-15 of the Arneric Declaration and Tables I and II attached thereto relate to inhibition constants of compounds (including (S,S) reboxetine) for various monoamine transporter and receptor sites, and the selectivity of compounds for the norepinephrine transporter site over the serotonin transporter site and other transporter or receptor sites. These portions of the Arneric declaration are discussed in detail, below, following a general

description of the significance of inhibition constants and selectivity. The data and statements presented in Dr. Arneric's declaration are factual evidence that the claimed methods would result in diminished adverse side effects.

The concentration of a compound required to inhibit 50% of the specific binding at a transporter or receptor site (i.e., IC_{50}) can be determined with radioligand binding assays by a non-linear, least square, regression analysis. This concentration (IC_{50}) is converted to an inhibition constant (K_i) utilizing the Cheng-Prusoff equation, which is shown as Equation 1, below, wherein [L] is the concentration of free radioligand used in the assay, and [K_d] is the dissociation constant of the radioligand for the transporter or receptor site:

$$K_i = \frac{IC_{50}}{\left(1 + \frac{[L]}{[K_d]}\right)}$$

Equation 1

See Y. Cheng and W.H. Prusoff (1973) *Biochem. Pharmacol.* **22**:3099-3108. The inhibition constant (K_i) is the concentration of the compound in the assay, which would occupy 50% of the transporter or receptor sites if no radioligand were present. Thus, the lower the inhibition constant (K_i) for a particular compound at a particular transporter or receptor site, the more potent the compound is at inhibiting reuptake at the site (e.g., the smaller the dose needed to induce an effect at the site). Conversely, the higher the inhibition constant (K_i) for a particular compound at a particular transporter or receptor site, the less potent that compound is at inhibiting reuptake at the site (e.g., the larger the dose needed to induce an effect at the site).

Inhibition constants can be used to make meaningful comparisons of compounds. For example, the selectivity of a particular compound favoring reuptake inhibition at one transporter or receptor site (*A*) relative to a second transporter or receptor site (*B*) can be determined by dividing the inhibition constants of the compound for the two sites, as shown in Equation 2, below, wherein *S* refers to the selectivity of the compound favoring reuptake inhibition at site *A* relative to site *B*:

$$S_{A/B} = \frac{(K_i)_A}{(K_i)_B}$$

Equation 2

See generally, the Specification at p. 30, line 28, to p. 32, line 24. In the foregoing equation, the selectivity (*S*) is a dimensionless number, where a value equal to one represents no selectivity (i.e., the compound exhibits equal affinity for both sites), values greater than one represent greater selectivity for site *B*, and values less than one represent greater selectivity for site *A*. *See* the Arneric Declaration, at ¶ 8. Thus, a compound's high selectivity favoring reuptake inhibition at a first transporter or receptor site (*A*) relative to a second transporter or

receptor site (*B*) reveals that the compound is not likely to inhibit reuptake at the first site (*A*) and, therefore, is not likely to cause (side) effects associated with reuptake inhibition at the first site (*A*).

Dr. Arneric's declaration includes two tables, which are discussed in paragraphs 8-15 therein. Table I of the declaration reports inhibition constants of different compounds for various monoamine transporter and receptor sites. The inhibition constants were obtained or determined in the manner set forth in paragraphs 12-15 of the declaration. Table II reports the inhibition constants of the same compounds relative to two sites — the norepinephrine and serotonin transporter sites — and also reports the selectivity of each compound for the norepinephrine transporter site and the serotonin transporter site. *See id.* at ¶ 8 and Table II. Though not shown in either of the tables, the selectivity of each compound for the norepinephrine transporter site over the other monoamine transporter and receptor sites (i.e., 5-HT_{2A}, H_1, α_1-adrenergic, and muscarinic) can be easily calculated based on Equation 2, above.

The data reported in Tables I and II for (S,S) reboxetine stand in stark contrast to the corresponding data for desipramine and amitriptyline. *See id.* at ¶ 10 and Table II. Specifically, (S,S) reboxetine exhibits surprisingly exceptional selectivity (>15,000) for the norepinephrine transporter site over that of the serotonin transporter site. (*Id.*) In contrast, amitriptyline and desipramine each exhibit a selectivity (1.8 and 430, respectively) that is magnitudes less than that exhibited by (S,S) reboxetine. *See id.* at Table II.

(b) The Ratcliffe Declaration

Attached hereto as Appendix "B" is a copy of a "Statutory Declaration" of Dr. Sian Louise Ratcliffe, which was recently filed in the European Patent Office during prosecution of European patent application No. 00941659.5, which is the European regional phase of the international counterpart to the current application. Although the declaration was submitted in connection with a foreign counterpart application, the text of the foreign counterpart application is identical to that of the current application and, therefore, the subject matter disclosed in the foreign counterpart application is identical to that disclosed in the current application.

Paragraphs 1-5 of Dr. Ratcliffe's declaration describe her education and work experience. Specifically, Dr. Ratcliffe has undergraduate and graduate degrees in physiology and pharmacology (including a Ph.D. in pharmacology she received in 1996 from the University of Cambridge). Since 2000, Dr. Ratcliffe has been employed by the successor-in-interest to the assignee of the current application where she is and has been responsible for, *inter alia*, clinical safety assessment for novel psychiatry and neuropathic pain treatments. Dr. Ratcliffe is qualified to comment on the subject matter disclosed in the current application.

Paragraph 8 of Dr. Ratcliffe's declaration describes a quality safety review that scrutinized the tolerability elderly patients exhibit toward the administration of (S,S) reboxetine as opposed to a commercially-available (racemic) reboxetine (specifically, EDRONAX®), and paragraphs 6 and 7 describe Dr. Ratcliffe's conclusions regarding the review. Dr. Ratcliffe's declaration refers to post-herpetic neuralgia ("PHN") and diabetic painful neuropathy ("DPN"), which are subclasses of peripheral neuropathy.

Two equivalent elderly patient populations were part of the quality safety review. One population suffered from a form of peripheral neuropathy (specifically, post-herpetic neuralgia ("PHN")) and were administered doses of (S,S) reboxetine, while a second population suffered from major depressive disorder ("MDD") and were administered doses of EDRONAX®. Dr. Ratcliffe declares that patients taking EDRONAX® reported tachycardia at nearly four times the frequency as compared with patients taking equivalent doses of (S,S) reboxetine. Dr. Ratcliffe further declares that incidences of the following adverse side effects were more frequent in the population taking EDRONAX® than in the population taking (S,S) reboxetine: term palpitation(s), dry mouth, hyperhidrosis (sweating), and anorexia/loss of appetite. *See generally*, the Ratcliffe Declaration, at ¶s 8.3 and 8.4 (and Tables 1 and 2 discussed therein). Dr. Ratcliffe also declares that "the lower frequency of palpitations/tachycardia reported in the current PHN study with [(S,S) reboxetine] is expected to be of clinical importance in the chronic pain population, given that patients with chronic pain may well have autonomic neuropathy (ie in diabetic painful neuropathy [DPN]), which is associated with palpitations." *Id.* at ¶ 8.4 (citation omitted).

3. The § 112, ¶ 1, Non-Enablement Rejection Is Traversed

The Patent Office's action does not provide a "reasonable" basis to question the enablement the patent application provides for the claimed invention. *In re Wright*, 999 F.2d at 1561-62 (stating that the Patent Office must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). Even if one were to conclude, however, that the action does provide a reasonable explanation questioning enablement, a fair analysis of the *Wands* factors would compel a conclusion that the patent application describes the claimed invention in compliance with § 112, ¶ 1. That conclusion also would be supported by the post application-filing evidence of enablement.

(a) The Patent Office Has Not Satisfied Its Burden of Establishing a Reasonable Basis to Question Enablement

The action provides no reasonable explanation as to why the scope of the claimed invention is not adequately enabled by the patent application. The action alleges facts without citing to any evidence. For example, the action alleges as fact that a "skilled artisan would expect the interaction of a particular compound in the prevention or treatment of this

particular neurological disorder [i.e., peripheral neuropathy] to be very specific and highly unpredictable absent a clear understanding of the structural and biochemical basis for the administration of a particular compound." *See* the action at pp. 4-5. The action identifies no evidence in support of this allegation.

The action also implies conclusions without citation to authority. For example, the action asserts that the patent application provides neither "working examples directed to the treatment or prevention of peripheral neuropathy," nor "examples to support or suggest a successful therapeutic regimen," implying that compliance with the enablement requirement requires the disclosure of such examples. *See* the Action at p. 4. Aside from whether the assertions are true and contrary to its implications, compliance with the enablement requirement *does not* turn on whether the patent application discloses a working example. MPEP § 2164.02 (8th ed. Rev. 3, Aug. 2005).

The Patent Office *must* identify evidence and legal authority supporting its factual allegations and legal conclusions that the claimed invention is not adequately supported by the patent application:

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis [i.e., non-enablement] is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

In re Marzocchi, 439 F.2d at 223-24. Without such evidence and authority, the Patent Office cannot set forth a "reasonable" basis for questioning the enablement. Accordingly, the applicants request reconsideration and withdrawal of the non-enablement rejection on grounds that the action does not provide a "reasonable" basis to question the enablement the patent application provides for the claimed invention.

(b) Consideration of the Wands Factors Compels a Conclusion that the Patent Application Enables the Claimed Invention

Even if one were to conclude that the action provides a "reasonable" explanation questioning enablement, an analysis of the *Wands* factors considering the evidence as a whole would compel a conclusion that the patent application describes the claimed invention in compliance with § 112, ¶ 1. Furthermore, and in view of the post-application filing evidence of selectivity, efficacy, and diminished adverse side effects, the applicants respectfully but strongly traverse the § 112, ¶ 1, non-enablement rejection.

The non-enablement rejection was issued based on a claim scope that has been amended herein to cancel those claims (e.g., claim 38) reciting methods of preventing peripheral neuropathy. In view of the amendments, the breadth of the claims is defined by independent claims 1 and 39, which relate to methods of treating an individual suffering from peripheral neuropathy. These methods include administering a therapeutically effective amount of optically pure (S,S) reboxetine (or a pharmaceutically acceptable salt thereof) to the individual. *See, e.g.*, claim 1. Embodiments of these methods can diminish adverse side effects, when, for example, a total dose of about 0.1 to about 10 mg/day of the optically pure (S,S) reboxetine (or a pharmaceutically acceptable salt thereof) is administered to the individual. The action provides no independent bases for questioning the enablement of any claim dependent on either of claims 1 or 39. One of the benefits of the claimed invention is a substantial reduction in the customary daily dosage of commercially-available racemic reboxetine when using an optically pure (S,S) reboxetine. Another of the benefits is that the claimed treatment methods result in fewer undesirable adverse side effects associated with the treatment because of the high selectivity and potency of (S,S) reboxetine with respect to inhibiting the reuptake of norepinephrine. Consideration of the *Wands* factors relating to the breadth of the claimed invention and the nature of the invention lead to a conclusion that the breadth and the nature are not as expansive as suggested in the action, especially in view of the claim amendments.

A person skilled in the art to which the invention is most nearly connected to make and use the claimed invention includes, according to the action, a person having a Ph.D. with expertise in the area of neurology, which, according to the applicants, would include a person having a Ph.D. in pharmacology and experience in the neurosciences. *See* Section II.B.1(a), above.

The action (p. 4) alleges that the prior art "does not presently recognize methods of preventing peripheral neuropathy or means of diminishing the side effects of reboxetine therapy," that "this particular art is immature" and, therefore, "a more detailed description as to the means of practicing the claimed methods would reasonably be expected." *See* Section II.B.1(b), above. The action identifies no evidence supporting these allegations.

Contrary to those allegations, a person having a Ph.D. in pharmacology and experience in the neurosciences would understand common knowledge in the prior art that side effects of the administration of a neurological drug may be diminished where the drug selectively interacts with a limited number of neurotransporter and receptor sites (preferably a single site) and does not interact with other neurotransporter and receptor sites. Indeed, the current application identifies such prior art and states that highly-selective inhibition of reuptake at certain neurotransporter and receptor sites would avoid adverse side effects. *See, e.g.*, the Specification at p. 8, lines 11-24.

A person having a Ph.D. in pharmacology and experience in the neurosciences would readily recognize in the prior art's teachings that gabapentin can be used to manage pain-related responses in several models of neuropathic pain. *See, e.g.*, the Ratcliffe Declaration, ¶ 8.2 (referring to Appendix 5). Gabapentin is commercially-available as Neurontin®, which is manufactured by Pfizer Inc. (the successor-in-interest to the assignee of the current application), and has been FDA-approved for the treatment of postherpetic neuralgia in adults. Thus, contrary to the suggestion in the action, the art suitably recognized the administration of gabapentin as one method of treating peripheral neuropathy. Moreover, the administration of a drug for the treatment of peripheral neuropathy is hardly "immature." For example, Rosner et al. (**1996**) *Clin. J. Pain* **12**:56-58 (copy attached as Appendix "C"), describes the successful use of gabapentin to treat peripheral neuropathy, including post-herpetic neuralgia, including dosing information. Indeed the published product insert for Neurontin® (copy attached hereto as Appendix "D") includes a description of how to administer Neurontin® to treat the approved indications (including post-herpetic neuropathy). Thus, the art recognized suitable formulations and dosing regimens to actively treat peripheral neuropathy.

Even if the treatment of peripheral neuropathy was "immature" as of the current application's filing date (or its priority benefit dates), the application provides ample direction to a person having a Ph.D. in pharmacology and experience in the neurosciences such that the person could prepare a suitable pharmaceutical composition containing (S,S) reboxetine and determine a suitable dosing regimen to treat peripheral neuropathy. Specifically, the specification describes *how to make* the composition recited in the claimed treatment methods at, for example, page 22, line 1, to page 24, line 11. The specification describes *how to practice* the claimed methods by specifying desirable and preferable daily doses at, for example, page 24, line 12, to page 25, line 3. The specification further states, at p. 25, line 29, to p. 26, line 2, that "the optimum daily dosage for each patient must be determined by a treating physician taking into account each patient's size, other medications which the patient is taking, identity and severity of the disorder, and all of the other circumstances of the patient." Moreover, there is ample disclosure in the prior art with respect to formulations and dosing regimens concerning the administration of racemic reboxetine, including the commercially-available forms of racemic reboxetine, like EDRONAX®.

Consideration of the *Wands* factors relating to the level of ordinary skill in the art, the state of the prior art, and the predictability in the art lead to a conclusion that a person having a Ph.D. in pharmacology and experience in the neurosciences cognizant of the prior art (and predictability in the prior art) would have had no reason to doubt whether the claimed methods would work.

The action also alleges that the patent application does not provide support for the "efficacy in the treatment or prevention of peripheral neuropathy, and diminishing adverse side effects following administration of (S,S) reboxetine," and that the "skilled artisan would expect the interaction of a particular compound in the prevention or treatment of this particular neurological disorder to be very specific and highly unpredictable absent a clear understanding of the structural and biochemical basis for the administration of a particular compound." *See* Section II.B.1(c), above. The action, again, identifies no evidence to support these allegations. More importantly, the action provides no reasonable basis on which to question the teachings in the application that selective, specific, and potent inhibition of norepinephrine reuptake would be effective to treat peripheral neuropathy and would result in diminished adverse side effects. Post-application filing experiments demonstrate that the claimed methods are effective to treat peripheral neuropathy and result in reduced incidences of adverse side effects. *See, e.g.*, the Ratcliffe Declaration; *see also*, the Arneric declaration.

Specifically, Drs. Arneric and Ratcliffe have Ph.D. degrees in pharmacology and have work experience in the neurosciences qualifying each to comment on the subject matter disclosed in the current application. Their declarations and conclusions further support the applicants' position that the claimed invention is enabled by the current application and refute any doubt the action might express regarding enablement. Specifically, the data reported in Table I of Dr. Arneric's declaration demonstrate that (S,S) reboxetine is a highly selective inhibitor of the norepinephrine transporter site having almost 25,000 fold selective response over other transporter/receptor sites (5-HT_{2A}, H_1, α_1-adrenergic, and muscarinic) believed to be responsible for adverse side effects. *See* the Arneric Declaration, at ¶ 11. Such high selectivity is not exhibited by any of the comparative compounds. Specifically, amitriptyline and desipramine each exhibit a selectivity for the norepinephrine transporter site over that of the other four monoamine transporter or receptor sites that, again, is magnitudes less than that exhibited by (S,S) reboxetine. *See id.* at Table I. Consequently, and in contrast to amitriptyline and desipramine (and their structurally-similar counterparts, nortriptyline and imipramine), one can definitively conclude that (S,S) reboxetine produces relief from peripheral neuropathy solely through its highly-selective interaction with the norepinephrine transporter site. Moreover, these data strongly suggest that the selectivity of (S,S) reboxetine should provide an overall improved safety and tolerability far beyond that of conventional tricyclic antidepressants.

The data reported in Dr. Ratcliffe's declaration support and supplement the data presented in Dr. Arneric's declaration. Specifically, the data reported in Dr. Ratcliffe's declaration demonstrate that patient populations taking (S,S) reboxetine suffer fewer (and less frequent) incidences of adverse side effects than populations taking commercially-available racemic reboxetine. Thus, the data and statements in the Arneric and Ratcliffe

declarations are factual evidence demonstrating the highly selective nature of (S,S) reboxetine (would) result in diminished occurrences of adverse side effects in chronic pain populations with post-herpetic neuralgia—effects that are associated with interactions with other transporter/receptor sites (5-HT_{2A}, H_1, α_1-adrenergic, and muscarinic).

Thus, a person having a Ph.D. in pharmacology and experience in the neurosciences would have been able to discern from the patent application (and also the knowledge in the art regarding commercially-available racemic reboxetine and the art's recognition of gabepentin to treat peripheral neuropathy) how to prepare a composition containing (S,S) reboxetine, how to achieve a suitable dosing regimen, and would have no reason to doubt the efficacy of the method disclosed and claimed in the application.

Finally, the action alleges that undue experimentation would be required to practice the claimed methods because the skilled artisan "would have to test extensively many adverse outcomes of therapy to discover which particular side effects respond to (S,S) reboxetine therapy." *See* Section II.B.1(d), above. Again, the action cites to no evidence in support of the allegation. The plain fact is that a person having a Ph.D. in pharmacology and experience in the neurosciences would not have to perform *any* tests to determine which side effects are responsive to the claimed treatment methods—simply performing the claimed method will result in reduced incidences of known-effects associated with serotonin reuptake inhibition, due to the highly-selective nature of (S,S) reboxetine. The claimed methods would diminish the side effects associated with serotonin reuptake inhibition (and reuptake at other transporter and receptor sites) because (S,S) reboxetine would not appreciably inhibit reuptake at these sites. Many of these effects are described in the application as previously identified herein and also in the supporting declarations of Drs. Arneric and Ratcliffe. Based on these and other teachings in the application, the skilled artisan would readily understand the claimed invention requires no experimentation (and certainly no undue experimentation) to appreciate its full breadth.

Based on all of the *Wands* factors and consideration of the evidence as a whole, it is respectfully submitted that the patent application includes a description of the claimed invention in compliance with § 112, ¶ 1, such that the rejection, upon reconsideration, should be withdrawn. In reconsidering whether the patent application includes an enabling disclosure of the claimed invention, the Patent Office must consider all evidence in the record (including the patent application), weighing evidence that confirms enablement against evidence that refutes enablement. *See In re Wands*, 858 F.2d at 737, 740. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the foregoing, entry of amendments to the specification, cancellation of claims 13 and 32-38, entry of the amendments to claims 1-9, 12, 14-17, 39, and 40, entry of new claims 54-67, consideration of the appended declarations, reconsideration and withdrawal of the rejection, and allowance of all pending claims 1-12, 14-17, 39, 40, and 54-67 are respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form or procedure in an effort to advance this application to allowance, the examiner is urged to contact the undersigned attorney.

Respectfully submitted,

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January 11, 2006

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